Remarks

The above Amendments and these Remarks are in reply to the Office Action mailed October 16, 2003. Applicants respectfully reiterate previous remarks and incorporate them herein fully by reference.

Claims 11-16, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C. §102(b) as anticipated and/or obvious under 35 U.S.C. §103 by Sara et al. (EP 0366638; published 02.05.90 "Sara"). The Examiner stated: "Sara discloses the administration of dipeptides ... and most preferably the tripeptide gly-pro-glu ... to treat neurodegenerative diseases and neural injury... thus teaching the "treatment of neural damage." Office Action, pate 3. Applicants respectfully traverse the rejections.

First, Applicants have amended claim 11 to explicitly include the priviso "wherein said peptide decreases cell death or degeneration" to make explicit that which was implicit in the preamble of the claim. Applicants have also added new claim 47.

I. Anticipation

Applicants submit that Sara does not anticipate, either expressly or inherently, the instant claims. MPEP 2131 states:

> A claim is anticipated only if **each and every element as set forth in the claim** is found, either expressly or inherently described, in a single prior art reference [references omitted]. **The identical invention must be shown in as complete detail** as is contained in the ... claim [reference omitted]. Emphasis added.

Applicants submit that neither the "identical invention" nor the "complete detail" were disclosed expressly or inherently, and that any such conclusion is legally unsupportable.

Express Anticipation

Sara does not disclose "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease comprising the step of administering to said mammal a neuroprotective amount of ... GPE," and therefore doesn't expressly disclose "each and every element as set forth in the claim" as required. In fact, Sara doesn't disclose any facts supporting a therapy to treat neurodegenerative

diseases and neural injury. Rather, Sara discloses "neuromodulation" in brain slices from normal animals. As pointed out in the previous response, the plain meanings of the terms "neuromodulation" and "neuroprotection" are different. In particular, "neuromodulation" is used by Sara in to mean a phenomenon distinctly different from "neuroprotection" of the Applicants' claims.

Inherent Anticipation

Applicants submit that Sara does not inherently anticipate the instant claims. MPEP 2112 states:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Emphasis added.

The Examiner refers to a standard for anticipation by inherency: *"the same peptide(s) to the same host(s) in the same amount(s) to treat the same diseases and/or neural injuries affecting the same neurons (glial cells/non-dopaminergic)."* Emphasis added.

Applicants respectfully submit that according to the MPEP 2112 or the standard articulated by the Examiner, Sara cannot inherently anticipate Applicants' claims because (1) the "host" is not the same and (2) the **treatment** is not of the "same disease."

1. The "Host" Is Not The Same

Sara's disclosed studies are in rat brain slices *in vitro*. The animals from which the brain slices were taken had not been exposed to any condition that could result in neurodegeneration, and thus, had not been exposed to "neural injury or disease." In contrast, the instant specification discloses (e.g., page 15, Experiment 3) results of experiments that make this point explicitly. Figure 3 demonstrates unequivocally that ligation of one carotid artery results in hypoxic-ischemic injury to the ipsilateral side of the brain. There is no disclosure in Sara of the use of GPE in any animal that had been so treated. Although Sara states that GPE might be useful to treat neurodegenerating conditions including Alzheimer's disease, Sara performed no studies on any diseased tissue. Therefore, the "host" can not "the same."

2. **The Disease and/or Neural Injuries Are Not The Same**

Sara discloses no "treatment" of any neurodegenerative condition. Sara discloses a potentiating effect of GPE on potassium-evoked neurotransmitter release in brain slices from normal rats. Although Sara suggests **possible uses** of GPE to cause "neuromodulation" in neurodegenerative conditions, there is **no enabling disclosure** that using GPE in normal animal tissues (as disclosed in *in vitro* brain slices) would have the same effect in animals subjected to neurodegenerative conditions.

Although the Examiner stated that "there is a much lower legal threshold regarding enablement of a reference, as compared to a patent application," the Examiner cited no authority that points out exactly what the legal threshold is, in particular for a foreign publication. If the Examiner is aware of a holding in support of the position, Applicants would appreciate having the reference.

Applicants note that the proper standard has been articulated by the Supreme Court.

> Patented inventions cannot be superseded by the mere introduction of a foreign publication of the kind, though of prior date, unless the **description** and drawings contain and exhibit a **substantial representation of the patented improvement**, in such full, clear, and exact terms as to **enable** any person skilled in the art of science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent. Mere **vague and general representations will not support such a defence** [sic], as the knowledge supposed to be derived from the publication must be sufficient to enable those skilled in the art or science to understand the nature and operation of the invention, and to carry it into practical use. Seymour v. Osborne 78 U.S. 516 (S. Ct. 1870); emphasis added.

First, the statements in Sara allegedly "disclose" the use of GPE to "treat neurodegeneration," but as pointed out above, there is no working example to support such a conclusion. Although Sara does include a working example of the effects of GPE on spinal cord reflexes *in vivo*, according to the methods paper describing the method (Z. Wiesenfeld-Hallin, Brain Research 372:172-175 (1986); copy enclosed herewith), Applicants note that the animals so studied **had no brains**, the animals having had their brains removed. "The rat was paralyzed with flaxedil i.a. artificially respired and decerebrated precollicularly by aspiration of cranial contents." Page 172, right column middle of the first full paragraph. Without any

brains, it is impossible for there to have been any effect of GPE as a "neuroprotective" agent at that location.

Applicants would like to point out that the art of pharmaceuticals, especially novel treatments for unmet medical needs is a "suspect art," in that a high degree of enablement is required to fulfill the requirements of patentability. Applicants submit that according to the Supreme Court in Seymour v. Osborne cited above, to be anticipatory, a reference must allow the public to "understand the nature and operation of the invention." Without any studies of tissues subjected to neurodegeneration, Sara cannot allow the public to "understand the nature and operation of the invention."

In contrast, Applicants' specification analyzed effects of GPE on the brains of animals subjected to controlled hypoxic ischemia. Moreover, although in both types of preparations (brain slices *in vitro* and decerebrate animals *in vivo*), the neurons and glial cells are destined to die, none of the studies could have revealed that GPE might have a neuroprotective effect. It was the Applicants' own specification that allows the public to "understand the nature and operation of the invention", namely that GPE "decreases cell death or degeneration" as in Claim 1.

Second, there is no need to provide any neuroprotective effect in normal cells. It is undisputed that the nerve cells of normal animals are alive and function "normally." Thus, the treatment of normal animals (e.g., Sara experiments) does not **necessarily** mean that the same treatment would have the same effect in animals subject to neurodegenerative conditions. Rather, neurodegeneration is inherently not normal.

Applicants submit that for the brain slices used in Sara to be considered the "same host" as necessary to conclude anticipation by inherency, the neurons and glial cells of Sara have to behave the same way as the corresponding cells in neurodegenerative conditions described in the Applicants' specification. The Examiner has provided no evidence that neural cells in neurodegenerating conditions respond to stimuli in the same fashion as do normal cells. Thus, there is no evidence that GPE would increase potassium evoked acetylcholine release in cells subject to neurodegeneration in the same fashion as disclosed by Sara. Sara made no such disclosure, and the Examiner has pointed to no reference or reasons why degenerating neurons or glial cells would **necessarily** behave the same, as would be required for anticipation by inherency.

Rather, Applicants assert that the "reference treatment" in Sara is merely an "invitation to experiment," which, under settled law is sufficient neither for obviousness nor for anticipation. Thus, Applicants assert that neither the "host" nor the "disease or condition" are the same. Therefore, even according to the Examiner's stated rule for anticipation by inherency, two of the three elements required to be the same are demonstrably different.

Missing Elements Defeat Anticipation by Inherency

Applicants respectfully submit that there are elements missing from the prior art necessary to link a "neuromodulator" effect of Sara 1 and "neuroprotective" effects of the instant application. Specifically, as pointed out in the previous response, reiterated and incorporated herein by reference, the words "neuromodulator" and "neuroprotective" do not have the same plain meanings, and are used differently in the documents themselves.

The Terms "Neuromodulator" and "Neuroprotective" are Used Differently By Sara and by Applicants

Sara uses the term "neuromodulator" in relation to results of acute, *in vitro* studies on brain slices (e.g., Example 2), in which GPE "is a **modulator** of neural function, thereby **stimulating or inhibiting** neural activity." Col. 1, lines 36-37; emphasis added. Sara 1 also discloses results of studies showing potentiation of spinal cord reflexes by GPE. Applicants assert that this use of "neuromodulator" is very close to the plain meaning above, namely "to regulate [neurotransmitter release or spinal reflexes] by or adjust to a certain measure or proportion [e.g., by GPE]." Thus, in the primary reference used to support the rejections, the meaning of "neuromodulation" is unambiguous.

However, even though the term "neuromodulation" is defined in Sara, Applicants respectfully submit that any "disclosure" in Sara must be interpreted in light of the mind of the Inventor at the time the application was filed. Currently settled law requires that conclusions of law (such as anticipation or obviousness) be based on the interpretation of the Inventor's language and the true meaning of the disclosure at issue. It is well known that terms can have several meanings, including the "plain meaning"

such as found in dictionary definitions and specialized meanings, reflecting the legal proposition that "a patentee may be his own lexicographer." Case law is replete with Court's determinations of what is meant by a term in a publication. Thus, Applicants respectfully disagree with the Examiner's assertion that reference to other works of the same author is either "tenuous at best" or "dubious at best." Rather, the subsequent publications by the Inventor clearly spell out what was meant by the term "neuromodulation" and are therefore highly probative of what was actually disclosed in Sara.

Another publication by Sara sheds light on the meaning of the term "neuromodulator." In the article, "Neuroactive Products of IGF-1 and IGF-2 Gene Expression in the CNS" Molecular Biology and Physiology of Insulin and Insulin-Like Growth Factors, Plenum Press, New York; pp 439 - 448 (1991)("Sara 3; copy provided in the previous Response as Appendix III) provides insight into the meaning of the term as used in Sara.

> GPE is believed to act as a **neuromodulator regulating neurotransmission.** GPE is the first example of the product of a growth factor gene having a **specific role in neurotransmission.** Page 443; emphasis added.

Applicants can find no indication in Sara 3 that the term "neuromodulation" had any other meaning, including meaning "neuroprotective" or any other term relating to enhancing survival of "glial cells or non-dopaminergic neurons."

In contrast, Applicants use the term "neuroprotective" refers to inhibition of cell death, as pointed out in claim 11: "A method for **protecting** glial **cells** or non-dopaminergic neural cells in a mammal **against death** from neural injury or disease comprising the step of administering to said mammal a **neuroprotective** amount of . . . GPE..." Emphasis added. Applicants submit that their use of "neuroprotection" is close to the above dictionary definition: "the act of protecting or the state of being protected; **preservation from injury or harm.** (2) **a thing, person, or group that protects:** *This vaccine is a protection against disease.* . . ." [Emphasis added, italics in original.]

Additionally, for Sara to inherently anticipate the instant claims, persons of ordinary skill would have to believe that **both** increasing **and** decreasing neurotransmitter release are **necessarily** linked to "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or

disease." In the previous Response, Applicants requested the Examiner to provide evidence that the conflicting results disclosed in Sara are both consistent with "neuroprotection." No such evidence was provided. Applicants again invite the Examiner, if he is aware of any evidence of such a reasonable belief, to provide such evidence, through either a prior art reference if available, or an Affidavit or a Declaration.

Sara is Not An Enabling Disclosure

Applicants respectfully reassert that Sara was not enabling of the instant invention. In the current Office Action, the Examiner stated: "[i]nitially, it is noted that there is a much lower legal threshold regarding enablement of a reference, as compared to a patent application." Office Action, page 12. However, the Examiner has provided no support for that proposition, and Applicants respectfully request the Examiner to either provide support for that legal proposition or to withdraw an unsupported assertion.

A. Examiner's Burden

Applicants submit that the Examiner has not met the burden of providing a *prima facie* case of anticipation by inherency.

> In relying upon the theory of inherency, the examiner must provide a basis **in fact and/or technical reasoning** to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the prior art. *Ex parte Levy* 17 USPQ2d 1461, 1464 (U.S.P.T.O.B.P.A.I. 1990); emphasis added, italics in original.

As explained above, Applicants submit given the different meanings of the terms, that the reasoning supplied is insufficient to permit the leap from "neuromodulation" to "neuroprotection." Further, given the differences in the "host" and the "disease," Applicants respectfully submit that the reasoning supplied is insufficient to permit a legally supportable leap from effects of GPE to increase potassium evoked acetylcholine release from normal rat neurons to effects of GPE to promote "neuroprotection" of "non-dopaminergic neurons and glial cells" subjected to "neural injury or disease."

B. Foreign Publications Must Be Enabling To Be Anticipatory

In re Wallace R. Gillam (17 C.C.P.A. 877 at 878, 37 F.2d 959, 1930 (CCPA 1930) ("Gillam") provides the standard by which foreign patents must be evaluated to be anticipatory references. The Gillam case arose from the U.S. Patent Office Board of Appeals affirmation of a final rejection over the principal reference, a French patent. In overturning the Board of Appeals decision, the CCPA held:

> In the case of foreign patents it has been held that they can not be measured as anticipatory by **what might be made out of them**, but only what is **clearly and definitely expressed** in them. [Citations omitted]; emphasis added.

Further support and rationale for the holding above is provided from the Second Circuit in *Permuttit Co. v. Harvey Laundry Co. et al.* 279 F.2d 713 (Court of Appeals, Second Circuit 1922) ("Permittut"):

> So, also, an invention, patented here, will not be defeated by a prior foreign patent, unless its descriptions and drawings contain or exhibit a substantial representation of the patented invention in full, clear, and exact terms, so as to enable a person skilled in the art or science to which it appertains, without the necessity fo making experiments, to practice the invention.

Additional support for the rational for the holding above is provided from the Circuit Court of Appeals of the Seventh Circuit in *General Electric Co. v. Hoskins Mfg. Co.* 224 F.2d (Seventh Circuit Court of Appeals 1915) ("General Electric"):

> The **prophetical suggestions in English patents** of what can be done, when **no one has ever tested**, by actual and hard experience and under the stress of competition, the truth of these suggestions, or the practical difficulties in the way of their accomplishment, or even whether the suggestions are feasible, do not carry conviction of the truth of these frequent and vague statements.

Although *Permittit* and *General Electric* cases are not binding on the U.S. Court of Appeals for the Federal Circuit, they demonstrate the consistent position that foreign references must be fully enabled.

Applicants submit that the "disclosure" in Sara relied upon by the Examiner consists only of textual references to prophetic examples in a suspect art, without any experimental support. First, Sara states "certain peptides exhibit neuromodulatory activity by **either stimulating or inhibiting** neural activity."

Column 1, lines 5-8. It is unclear from anything in Sara or any other source, how both "stimulating" and "inhibiting" neural activity could each be consistent with treating neurodegenerative conditions. At best, Sara shows the GPE has some effect on neurons. If the Examiner is aware of any reference that teaches how either stimulation or inhibition of nerves is associated with neuroprotection, the Applicants would appreciate having the citation and a copy.

Moreover, the only reference to "neurodegenerative conditions" is a listing of possible conditions, with no explanation as to how any desired therapeutic effect is to be obtained. Specifically, Sara does not disclose which conditions would benefit from "stimulating" neurotransmitter release and which conditions would benefit from "inhibiting" neurotransmitter release. Sara discloses (1) no experiments on neural survival, (2) no experiments in which GPE was used to treat any condition involving neurodegeneration or neural or glial cell death, (3) no long-term studies of any effect of GPE, (4) no experiments in which neural survival was measured, and (5) no link between acute *in vitro* studies on potassium-evoked acetylcholine release or spinal cord reflexes and survival of any cell type. Further, (6) none of the studies were described as being on brain slices from any animal that had been subjected to neural damage or disease. Thus, Applicants conclude that Sara did not describe any conception and reduction to practice of any "neuroprotective" effect of GPE, and therefore cannot anticipate the instant claims. Rather, based on Sara, any desired therapeutic effect is merely speculative and therefore not enabled.

Therefore, Applicants submit that Sara cannot inherently indicate that neuromodulation is useful for "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease" Although it may be possible that such an effect exists, such a **possibility** cannot sustain a rejection based on inherency. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." MPEP, Id. Thus, Applicants submit that a *prima facie* case for anticipation has not been made.

In light of the dearth of enabling disclosure about roles of GPE on neuroprotection, Applicants submit that Sara cannot anticipate the instant claims.

II. Obvi usness

A. Sara

Claims 11-17, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C. §103 as obvious over Sara. Applicants respectfully submit that no *prima facie* case for obviousness has been made.

> To establish a *prima facie* case for obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a **reasonable expectation of success.** Finally, the prior art reference must **teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and **not based on applicant's disclosure.**

Applicants respectfully submit that the instant claims cannot be rendered obvious by Sara. As described above, Sara discloses that GPE either "stimulates or inhibits" neural activity and can potentiate spinal cord reflexes. However, Sara neither teaches nor suggests that GPE can be effective in "protecting glial cells or non-dopaminergic neural cells in a mammal against **death** from neural injury or disease." [Emphasis added.] Applicants therefore submit that Sara cannot render the instant claims obvious.

Thus, at best, the experiments disclosed in Sara provide the legally discredited "invitation to experiment" or "obvious to try" standard of obviousness, which is not the law. Specifically, Sara's findings might stimulate one to inquire about possible effects of GPE on brain slices from brain-damaged or brain-diseased animals, but could not have provided a reasonable basis to conclude that acute effects of GPE on neurotransmitter release inherently discloses any property of GPE to promote "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." Rather, for Sara to render the instant claims obvious, **both potentiation and inhibition** of acetylcholine release would have to relate to "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease".

Regarding the fact that a *prima facie* case for obviousness requires a "motive to modify the reference" and "reasonable likelihood of success," Applicants note that a subsequently published article by Sara ("The Biological Role of Truncated Insulin-like Growth Factor-1 and the Tripeptide GPE in the

Central Nervous System" Annals of the New York Academy of Science; pp: 183 - 191 (1991); "Sara 2"; copy enclosed with the prior Response as Appendix II) actually teaches away from Applicants' claims.

> Extensive *in vivo* studies have **not revealed any growth-promoting activity of GPE**.... As shown in Figure 4, no significant growth effects, including tail length and organ weights, were observed. Page 187, middle of first full paragraph.

Thus, Applicants submit that at the time of publication of Sara 2, the first inventor of Sara could not have had a reasonable belief that GPE could be a growth modulator, and thus that there would be no reasonable likelihood of success at achieving the Applicants' invention. In the absence of a reasonable belief by the primary inventor (Sara), Applicants submit that no person of ordinary skill could have such a reasonable belief. Applicants submit that both Sara and Sara 2 considered GPE to be an agent that acted on neurotransmitter receptors and not as a growth promoting hormone. Because Sara was silent about any effects of GPE to promote "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease," Applicants submit that at the time of publication of Sara 1, there was neither motive nor a reasonable belief that GPE could so act.

Additionally, Sara 3 provides insight into the teaching of Sara 1. In particular:

> The peptide products from expression of the IGF-1 gene in the brain, namely truncated IGF-1 and GPE, appear to induce biological responses **via two separate mechanisms**. The action of truncated IGF-1 is mediated via the IGF-1 receptor. GPE does not cross-react with the IGF-1 receptor, but rather in the NMDA receptor, and possibly an additional, as yet undefined, mechanism.
>
> ...
>
> Instead, GPE cross-reacts in the NMDA (N-methyl-D-aspartate) receptor which is a subtype of receptors for the major excitatory amino acid neurotransmitter glutamate.... .GPE **potentiates the release of dopamine** via interaction in the NMDA receptor.
>
> ...
>
> In conclusion, . . . GPE is believed to act as a **neuromodulator regulating neurotransmission**. GPE is the first example of the product of a growth factor gene having a **specific role in neurotransmission**. Page 443; emphasis added.

Applicants are not aware of any portion of any of Sara 2 or Sara 3 that teach or suggest that GPE could be neuroprotective, and therefore teach away from using GPE for "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease."

The Examiner found the above argument non-persuasive because "these references are not being relied upon in the above rejection." Office Action, page 14, third full paragraph. Applicants note that persons of ordinary skill are presumed to be aware of all art pertaining to an invention.

Further, Sara 2 and Sara 3 provide evidence of several factors cited in *Graham v. John Deere*. In particular, "unexpected results," "long felt need," "failure of others" and "skepticism of others." Had Sara been enabling for claims to the use of GPE for neuroprotection, Sara would not have had to mention in a subsequent publication: "[e]xtensive *in vivo* studies have **not revealed any growth-promoting activity of GPE. . .**"

Rather, Applicants respectfully submit that the motive and reasonable likelihood of success were provided by the Applicant's own instant disclosure, and that any obviousness rejection must have been based on hindsight reconstruction.

B. Sara in View of Sibalis

Claims 11-17, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C.§103 over Sara (Sara 1) in view of Sibalis (U.S. 5,032,109; "Sibalis").

Applicants incorporate herein the discussions presented above for Sara.

The Examiner stated that Sibalis teaches transdermal delivery of "polypeptides containing about three to 20 alphaamino acid units." However, Applicants can find no teaching in Sibalis and Sara together of any method for "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." Thus, the combination of Sara and Sibalis does not disclose all the limitations of the pending claims with a reasonable likelihood of success, and thus cannot render Applicants' claims obvious. Applicants therefore urge the Examiner to reconsider the rejection and find the claims allowable.

C. **Sara in View of Gluckman**

Claims 11-16 and 18-46 stand rejected under 35 U.S.C. §103 over Sara in view of Gluckman (WO 93/02695; "Gluckman").

Applicants incorporate herein the discussions presented above for Sara.

The Examiner stated that Gluckman teaches "a method for treatment or prevention of CNS damage caused by neurodegenerative disease and trauma which primarily causes damage to glia and/or other non-cholinergic cells in the CNS." Office Action, page 9, bottom paragraph. The Examiner also stated "It is noteworthy that the Gly-Pro-Glu peptide, as presently claimed, is derived from the N-terminal three amino acids of IGF-1 peptide." Office Action, page 10 bottom of first paragraph.

Applicants note that Gluckman does not disclose "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of... GPE ..." as in claim 11. Nowhere in either Sara nor Gluckman, nor in the combination of Sara and Gluckman together, is any teaching of the use of GPE as in claim 11. Thus, the combination of Sara and Gluckman does not disclose all the limitations of the pending claims with a reasonable likelihood of success, and thus cannot render Applicants' claims obvious.

Although GPE is the N-terminal tripeptide of IGF-1, both Sara 2 and Gluckman teach away from GPE as a neuroprotective agent. First, Gluckman teaches that IGF-1 is neuroprotective (e.g., see Abstract and Summary of the Invention, page 3, first paragraph). Next, Sara 2 states: "The aminoterminal tripeptide of IGF-1, GPE, displays a different range of biological actions compared to truncated IGF-1. These effects are not mediated by IGF-1 receptors. As shown in Figure 3, GPE fails to cross-react with the IGF-1 receptor and does not influence the binding of either intact or truncated IGF1 to the receptor." Page 187, middle paragraph, middle section. Thus, Applicants submit that one or ordinary skill in the art would view Sara in the same light as Sara 2, and when combined with Gluckman, would provide no motive to nor a reasonable believe in the success of, any study to determine whether GPE had neuroprotective properties.

Rather, Applicants submit that the instant disclosure provided the link between IGF-1, GPE and "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of... GPE ..." as in claim 11. "To date, there

has been no enabling reference in the prior art to the manipulation of the cleaved tripeptide GPE itself to prevent or treat CNS injury or disease leading to CNS damage *in vivo*." Specification, page 3, third paragraph. Using such hindsight reconstruction to argue for unpatentability is impermissible under 35 U.S.C. §103, the MPEP and case law. Applicants therefore urge the Examiner to reconsider the rejections and find the claims allowable.

III. Conclusions

Applicants respectfully submit that there is insufficient showing that Sara either expressly or inherently anticipates or renders the instant claims obvious and that no *prima facie* for either rejection has been made. Even if there were a *prima facie* case for obviousness, consideration of *Graham* factors leads to the conclusion that prior to Applicants' disclosure, there were long felt need, failure of other, unexpected results, and "skepticism of others," and Applicants respectfully request the Examiner to provide the missing evidence necessary to make a *prima facie* showing of either anticipation or obviousness. In the absence of such evidence, either through citation of a publication or through an Affidavit or Declaration, Applicants request the Examiner to reconsider the rejections and find the claims allowable.

Further, Applicants conclude that no combination of Sara, Sibalis or Gluckman taught or suggested, with a reasonable likelihood of success, all limitations of the instant claims, and therefore, that no combination of those references renders the instant claim obvious. In fact, Sara 2 actually taught away from the instant claims. Because Sara 2 was published after Sara 1, any interpretation of Sara to teach "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of... GPE..." is not supported. Even if Sara were interpreted to suggest that GPE is neuroprotective, Sara 2 is unambiguously in conflict, and a worker of ordinary skill would not have any clear guidance, and thus would not have been led by the prior art to find the instant claim obvious.

In light of the above, it is respectfully submitted that all of the claims now pending in the subject patent application should be allowable, and a Notice of Allowance is requested. The Examiner is

respectfully requested to telephone the undersigned if he can assist in any way in expediting issuance of a patent.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 06-1325 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: December 16, 2003 By: D. Benjamin Borson

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